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## 5. Introduction

The BRCA1 gene was mapped to chromosome 17q in 1990 by Mary- Claire King and colleagues. Shortly thereafter, Dr. Narod was able to confirm that BRCA1 was the gene for the breast-ovarian cancer syndrome as well. From 1990-1994, a series of experiments in several laboratories confirmed that BRCA1 was the gene responsible for the majority of families with multiple cases of breast and ovarian cancer. The risk of breast cancer for women who carry a mutant copy of this gene is 87% to age 70. The risk of ovarian cancer is 50%. The purpose of the present study is to clone the BRCA1 gene and to identify the range of mutations present in the families with the breast ovarian cancer syndrome.

The objectives of the study were stated as follows:

- 1) To identify highly informative polymorphic markers in the region of BRCA1.
- 2) To type linked breast and ovarian cancer families with these markers and to identify all of the crossovers which provide information about the minimum region of chromosome 17 containing BRCA1.
- 3) To produce a physical map of the minimum region by identifying a series of overlapping contiguous fragments of YAC DNA inserts that span the region.
- 4) To identify the coding sequences in the cloned YACs and to assay the expression of these genes in normal breast and ovary and in tumors derived from these tissues.
- 5) To test genes identified to be in the minimum region for rearrangements and for point mutations that may be associated with cancer predisposition in the families.
- 6) To sequence the BRCA1 gene in our panel of 100 hereditary breast and breast-ovarian cancer families and to identify the range of mutations in this gene.
- 7) To evaluate the association between particular mutations and cancer patterns in the panel of families.
- 8) To sequence the BRCA1 gene in the constitutional DNA panel of women with apparently sporadic breast and ovarian cancers.
- 9) To sequence the BRCA1 gene in the tumour DNA panel of women with apparently sporadic breast and ovarian cancers.

Objectives 1 to 5 have been accomplished through a collaboration of Dr. Narod and other researchers.

Objectives 6 and 7 have been reached in 1996. These results do not support the hypothesis that different mutations are associated with different phenotypes. Rather, it appears that the other genes will be more important in modifying genetic risk.

Objective 8 is in progress for Ashkenazi Jewish women.

Objective 9 has been studied by others. It is found that mutations in BRCA1 are not frequent in sporadic breast and ovarian tumours. The great majority of mutations detected have been germline (hereditary) mutations. This objective will not be pursued further.

Details of the progress of these individual objectives is provided below:

## 6. Body

### 6.0 Overview

The goal of the current study was to identify the BRCA1 gene through positional cloning. The approach involved a combination of genetic mapping and physical mapping, leading to the identification of candidate genes from chromosome 17q. Through a collaborative effort the BRCA1 gene was cloned in October 1994 (Miki et al, 1994). Dr. Narod was a contributing partner in this collaboration.

The cloning of the BRCA1 gene took place in year one of the grant period of Dr Narod. Dr. Narod has capitalized on the early results and has gone on to use these results to investigate several aspects of the population genetics of BRCA1, including: establishing the range of BRCA1 mutations in breast-ovary families; 2) establishing mutation/haplotype correlations; 3) establishing the existence of predominant mutations in ethnic subgroups; 4) establishing the proportion of breast cancer families due to BRCA1; 5) establishing genetic and non-genetic modifiers of BRCA1 penetrance.

This body of work has contributed to the completion of 20 papers which are listed in the References below and a copy of each is provided in the Appendix. Dr. Narod is the first author on three papers, is the senior author on five other papers and is a contributing author on the 12 remaining papers.

### 6.1 Genetic mapping of BRCA1

In 1994 the region of assignment was established to be an interval of 1.2 kb surrounding the gene for estradiol dehydrogenase (EDH17B). This was a key candidate gene and had been tentatively ruled out by direct sequence analysis, but not by linkage analysis. By examining a genetic recombinant in a 45-year old woman in a family with 10 cases of early-onset breast cancer and a single case of ovarian cancer it was possible to map the BRCA1 gene distal to the

EDH17B locus (Tonin et al, 1994). This became the proximal boundary for BRCA1. Through a collaboration with the University of Utah, a distal boundary for the BRCA1 interval (D17S78) was established. These two markers formed the genetic interval of assignment of BRCA1, a region of 600kb.

## 6.2 Physical mapping of BRCA1

At the same time as the construction of the genetic map, a physical map of cloned DNA fragments (YACS) was under construction in the laboratory of Dr Narod, in collaboration with Dr. J. Rommens of the Hospital for Sick Children Toronto for the region corresponding to the genetic map (Rommens et al, 1995). This physical map was used to identify 30 unique cDNA fragments, by hybridisation of RNA libraries to immobilized YACs. These 30 clones were aligned to form ten transcription units. Several known and unknown genes were mapped by this process, including gamma-tubulin and the Ki antigen gene. None of these 30 clones was the BRCA1 gene. The construction of the physical map using the YAC library took place in the laboratory of Dr Narod, the retrieval of gene fragments took place in the laboratory of Dr. Rommens and the sequencing of the fragments took place in the laboratory of Dr. Jacques Simard.

## 6.3 Identification of BRCA1 mutations

The BRCA1 gene was identified in September 1994. Dr. Narod has participated in four studies of mutation analysis of families with hereditary breast cancer and with the breast ovarian cancer syndrome, and has contributed to several consortium analyses. In the first study, 14 BRCA1 mutations were identified in 30 Canadian families (Simard et al, 1994). This experiment was noteworthy in that the first examples of recurrent mutations were identified in the Canadian families. In four families the mutation 185 del (AG) was found. This is now the most commonly reported BRCA1 mutation. In another four families a second mutation, 5382 ins C, was found. By creating genetic haplotypes it was evident that the common mutations were seen in the context of a common haplotype. This implies that the patients with these mutations, although previously have been believed to be unrelated, have a common ancestor. A second set of Canadian families has now been screened for mutations. In this set of 30 breast cancer families an additional four mutations have been found (Durocher et al, in press). Three of these mutations have been seen before. The other is a novel mutation which appears to be unique to French- Canadians. This mutation has now been detected in an additional 12 French- Canadian families among 69 screened. In total, BRCA1 mutations have been identified in 50 Canadian families.

A further 50 breast-ovarian cancer families from Creighton University have been characterized by a combination of linkage analysis, haplotype analysis and direct sequencing in collaboration with Dr. Henry Lynch (Omaha, Nebraska) and Dr. Gilbert Lenoir (Lyon, France). These families have been ascertained by Dr. Lynch. The linkage and haplotype analysis was performed by Dr.

Narod in Montreal. The sequencing for BRCA1 mutations was done by Dr. Lenoir in Lyon. In the first report, there were 16 BRCA1 mutations identified in the 20 families from Creighton University (Serova et al, 1996). A second set of 30 families from Creighton University have been characterized for BRCA1 and BRCA2 mutations (Serova et al, submitted). Thirteen mutations were identified.

The linkage and mutation data that is generated for the Creighton families is used for a genetic counselling evaluation project that is also funded by the Department of the Army (Caryn Lerman PI). Dr. Narod provides the risk assessment data used for this study and has to date provided DNA-based risk assessments to over 250 individuals in these 20 families. The funds for the laboratory component of this study are derived from the current project The Cloning of the BRCA1 Gene. Dr Narod does not receive any additional funding for this project from Dr. Lerman. Several factors were found to predict utilization of genetic testing in this study, including sex, educational status and insurance coverage (Lerman et al, 1996).

#### 6.4 Genetic epidemiology of BRCA1

After the cloning of BRCA1 much of the effort in Dr. Narod laboratory focused on studies of the range and frequency of BRCA1 mutations in the population and the use of this information for the rapid detection of mutations.

In the paper of Simard et al (1994) there were four families reported with the 185 del AG mutation. It was noted that all of these are of Ashkenazi Jewish origin. This finding was extended to include two additional families and it was noted that these were Ashkenazi as well (Tonin et al, 1995). This specific association has now been seen in over twenty families worldwide. It has been found by another research group that this mutation may be present in 1% of Ashkenazi Jews and this story has been the subject of much media attention worldwide. In a collaborative study BRCA1 mutations were found for 94 of 245 Jewish families with two or more cases of breast cancer (Tonin et al, in press).

One of the critical questions is to estimate the proportion of Jewish women with breast and ovarian cancer who are carriers of the del AG mutation. To answer this question a study of 300 Jewish patients with ovarian cancer is planned. These patients are selected from the list of all living patients with epithelial ovarian cancer at each of 10 hospitals in Canada and the USA. Each is interviewed about family history and reproductive history and a blood sample is obtained to screen for the 185 del AG and the 5382 insC mutations. A control sample of 400 Jewish women will be interviewed about family and reproductive histories (no blood samples obtained from controls). Dr. Narod has received a supplement of 37,000 dollars from the National Action Committee on Breast Cancer to perform this study. Of the first 80 women enrolled in this study there have been 21 mutations detected, including twelve women with 185delAG mutations and nine with 5382insC mutations.

A similar study has been started on French Canadian women. 250 French-Canadian women



with ovarian cancer have been selected from three Quebec hospitals. To date, 160 women have been enrolled and blood samples are now available on these. BRCA1 mutations will be sought in the familial cases. If recurrent mutations are found, the entire study group of 250 women will be screened for the recurrent mutations. The goal of this study is to identify the frequent mutations in this ethnic group in order to plan for provincial based screening program for hereditary breast and ovarian cancer. Two recurrent BRCA1 mutations in French-Canadian families have been identified.

Dr. Narod analysed and prepared a report of data from 145 breast-ovarian cancer families on behalf of the Breast Cancer Linkage Consortium (Narod et al, 1995a). The study estimated that 76% of breast ovary cancer families were attributable to BRCA1. If the family had no cases of male breast cancer and two or more cases of ovarian cancer, the estimated linked proportion was 92%. After the BRCA1 gene was cloned and BRCA2 was mapped it was possible to reanalyse the data from the 145 families (Narod et al, 1995b). There were 10 apparently unlinked families in the original report. BRCA1 mutations were subsequently identified in three families and the other seven families are linked to BRCA2. None of the original 145 families is convincingly unlinked to BRCA1 and to BRCA2.

Not all carriers of BRCA1 mutations develop cancer, and for those who do, the age of onset varies. Some women develop breast cancer and other develop ovarian cancer. In an attempt to determine the relevant genetic and non-genetic factors which contribute to the clinical expression of the BRCA1 gene, Dr. Narod has collected DNA samples and associated clinical information on over 300 female carriers of BRCA1 mutations. By using of a historical cohort design, and a Cox proportional hazards analysis, it has been possible to study the effect of modifying genes and of reproductive factors on cancer penetrance (Narod et al, 1995c, Phelan et al, 1996). It was found that parity is an important risk modifier - each additional birth decreases the risk of breast cancer by 15%, but increases the risk of ovarian cancer by 40%. However, the risk of ovarian cancer is decreased by a late birth. There was a strong cohort effect present for both cancer types; the risk of breast and ovarian cancer is roughly double for women born after 1930 than for women born before 1930. Several genetic polymorphisms have been evaluated to see if they modify the penetrance of BRCA1. The presence of a rare allele of the HRAS1 polymorphism is associated with a 2.85-fold increase in the risk of ovarian cancer in the cohort of 307 BRCA1 carries ( $p = 0.002$ ). There was no effect on the penetrance of breast cancer by the HRAS1 locus. Additional genes that are being evaluated for modifying effects on this cohort include epoxide hydrolase and GSTM1.

In this panel of 80 families there was no significant association between mutation type or mutation position and the risk of breast or ovarian cancer. The mutations in the 3' end of the gene were associated with a 40% reduction in ovarian cancer risk, but this difference was not significant ( $p = 0.28$ ).

## 7. Conclusions

Through a combined linkage and physical mapping approach Dr. Narod contributed to the cloning of the BRCA1 gene in late 1994. The identification of this gene has led to many important questions regarding the biology of the gene, the population genetics of BRCA1 mutations and clinical management of women who are identified to be carriers of BRCA1 mutations. Dr. Narod's efforts have been focussed on establishing the presence of genetic and non-genetic modifiers of cancer risk in BRCA1 carriers.

## 8. References

1. Miki et al, and 44 others, including SA Narod. A strong candidate gene for the breast and ovarian cancer susceptibility gene, BRCA1. *Science* (1994) 266, 66-71.
2. Simard J, Tonin P, Durocher F, Morgan K, Rommens J, Gingras S et al Common origins of BRCA1 mutations in Canadian breast and ovarian cancer families. *Nature Genetics* (1994) 8: 392-398.
3. Neuhausen SL, and 19 others, including Narod SA. A P1-based physical map of the BRCA1 region from D17S776 to D17S78. *Hum Mol Genet* (1994) 3, 1919-1926.
4. Tonin P, Serova O, Simard J, Lenoir G, Feunteun J, Morgan K, Lynch H, Narod SA. The gene for hereditary breast-ovarian, BRCA1 maps distal to EDH17B2 in chromosome region 17q12-21. (*Hum Molec Genet* (1994) 3, 1679-1682.
5. Narod SA, Ford D, Devilee P, Barkardottir RB, Lynch HT, Smith SA et al. An evaluation of genetic heterogeneity in 145 breast- ovarian cancer families. *Amer J Hum Genet* (1995a) 56:254-264.
6. Narod SA, Ford D, Devilee P, Barkardottir RB, Eyfjord J, Lenoir G, Serova O, Easton D, Goldgar D (1995b) Genetic heterogeneity of breast-ovarian cancer revisited. *Amer J Human Genet* (1995b) 57: 958-960.
7. Narod SA, Goldgar D, Cannon-Albright L, Weber B, Moslehi R, Ives E, Lenoir G, Lynch H. Risk modifiers in BRCA1 carriers. *International Journal of Cancer* (1995c) 64, 394-398
8. Rommens JM, Durocher F, McArthur J, Tonin P, Leblanc JF, Allen T, Samson C, Ferri L, Narod SA, Morgan K, Simard J. Generation of a transcription map of the HSD17B locus centromeric to BRCA1 at 17q21. *Genomics* (1995) 28, 530-542.
9. Shattuck-Eidens D, McClure M, Simard J, Labrie F, Narod SA, Couch F et al. A collaborative survey of 80 mutations in the BRCA1 breast and ovarian cancer susceptibility gene. Implications for presymptomatic testing and screening. *J Amer Medic Assoc* (1995) 273:535-541.
10. Tonin P, Serova O, Lenoir G, Lynch HT, Durocher F, Simard J, Morgan K, Narod SA. BRCA1 mutations in Ashkenazi Jewish women. *American Journal of Human Genetics* (1995) 57, 189.
11. Tonin P, Moslehi R, Normand T, Vivier A, Miller S, Gisnburg O, Cutler C, Margolese R, McGillivray B, Labrie F, Simard J, Narod SA. Linkage analysis of 13 Canadian breast and breast- ovarian cancer families. *Human Genetics* (1995) 5, 545-550.

12. Cornelis RS and 21 others, including Narod SA. High allele loss rates at 17q12-q21 in breast and ovarian tumours from BRCA1- linked families. *Genes Chromosomes and Cancer* (1995) 13, 203-210.
13. Neuhausen SL and 23 others, including Narod SA. Haplotype and phenotype analysis of six recurrent BRCA1 mutations in 61 families, results of an international study. *Am J Hum Genet* (1996) 58, 271-280.
14. Phelan CM, Rebbeck TR, Weber BL, Devilee P, Lynch HT, Lenoir GM, Stratton MR, Easton DF, Ruttledge MH, Larsson C, Goldgar DE, Narod SA. The risk of ovarian cancer in BRCA1 carriers is modified by the HRAS1 locus. *Nature Genetics* (1996) 12, 309-311.
15. Marcus JN, Watson P, Page DL, Narod SA, Lenoir GM, Tonin P, Linder-Stephenson L, Salerno G, Conway TA, Lynch HT. Hereditary breast cancer; pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage. *Cancer* (1996) 77, 697-709.
16. Serova O, Narod SA, Tonin P, Feunteun J, Sylla B, Lynch HT, Lenoir GM. BRCA1 mutation analysis of 20 breast-ovarian cancer families. *American Journal of Human Genetics* (1996) 58, 42-51.
17. Lerman C, Narod S, Schulman K, Hughes C, et al. Predictors of utilization of BRCA1 testing in hereditary breast ovarian cancer families: implications for patient education and informed consent. *JAMA* (in press).
18. Durocher F, Tonin P, Shattuck-Eidens D, Skolnick M, Narod SA, Simard J. Mutation analysis of the BRCA1 gene in 24 families with cases of cancer of the breast ovary and multiple other sites *Mutation Res* (in press).
19. Tonin P and 26 others, incl. Narod SA. Frequency of recurrent BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer families. *Nature Med* (in press).
20. Serova O, Mazoyer S, Puget N, Dubois V, Tonin P, Shugart Y, Goldgar D, Narod SA, Lynch HT and Lenoir GM. Mutations in BRCA1 and BRCA2 in breast cancer families. Is there a third gene? *Am J Hum Genet* (submitted).

## 9. Appendices

N/A

## 11. Bibliography

1. Miki et al, and 44 others, including SA Narod. A strong candidate gene for the breast and ovarian cancer susceptibility gene, BRCA1. *Science* (1994) 266, 66-71.
2. Simard J, Tonin P, Durocher F, Morgan K, Rommens J, Gingras S et al Common origins of BRCA1 mutations in Canadian breast and ovarian cancer families. *Nature Genetics* (1994) 8: 392-398.
3. Neuhausen SL, and 19 others, including Narod SA. A P1-based physical map of the BRCA1 region from D17S776 to D17S78. *Hum Mol Genet* (1994) 3, 1919-1926.
4. Tonin P, Serova O, Simard J, Lenoir G, Feunteun J, Morgan K, Lynch H, Narod SA. The gene for hereditary breast-ovarian, BRCA1 maps distal to EDH17B2 in chromosome region 17q12-21. (*Hum Molec Genet* (1994) 3, 1679-1682.
5. Narod SA, Ford D, Devilee P, Barkardottir RB, Lynch HT, Smith SA et al. An evaluation of genetic heterogeneity in 145 breast- ovarian cancer families. *Amer J Hum Genet* (1995a) 56:254-264.
6. Narod SA, Ford D, Devilee P, Barkardottir RB, Eyfjord J, Lenoir G, Serova O, Easton D, Goldgar D (1995b) Genetic heterogeneity of breast-ovarian cancer revisited. *Amer J Human Genet* (1995b) 57: 958-960.
7. Narod SA, Goldgar D, Cannon-Albright L, Weber B, Moslehi R, Ives E, Lenoir G, Lynch H. Risk modifiers in BRCA1 carriers. *International Journal of Cancer* (1995c) 64, 394-398
8. Rommens JM, Durocher F, McArthur J, Tonin P, Leblanc JF, Allen T, Samson C, Ferri L, Narod SA, Morgan K, Simard J. Generation of a transcription map of the HSD17B locus centromeric to BRCA1 at 17q21. *Genomics* (1995) 28, 530-542.
9. Shattuck-Eidens D, McClure M, Simard J, Labrie F, Narod SA, Couch F et al. A collaborative survey of 80 mutations in the BRCA1 breast and ovarian cancer susceptibility gene. Implications for presymptomatic testing and screening. *J Amer Medic Assoc* (1995) 273:535-541.
10. Tonin P, Serova O, Lenoir G, Lynch HT, Durocher F, Simard J, Morgan K, Narod SA. BRCA1 mutations in Ashkenazi Jewish women. *American Journal of Human Genetics* (1995) 57, 189.
11. Tonin P, Moslehi R, Normand T, Vivier A, Miller S, Gisnburg O, Cutler C, Margolese R, McGillivray B, Labrie F, Simard J, Narod SA. Linkage analysis of 13 Canadian breast and breast- ovarian cancer families. *Human Genetics* (1995) 5, 545-550.

12. Cornelis RS and 21 others, including Narod SA. High allele loss rates at 17q12-q21 in breast and ovarian tumours from BRCA1- linked families. *Genes Chromosomes and Cancer* (1995) 13, 203-210.
13. Neuhausen SL and 23 others, including Narod SA. Haplotype and phenotype analysis of six recurrent BRCA1 mutations in 61 families, results of an international study. *Am J Hum Genet* (1996) 58, 271-280.
14. Phelan CM, Rebbeck TR, Weber BL, Devilee P, Lynch HT, Lenoir GM, Stratton MR, Easton DF, Ruttledge MH, Larsson C, Goldgar DE, Narod SA. The risk of ovarian cancer in BRCA1 carriers is modified by the HRAS1 locus. *Nature Genetics* (1996) 12, 309-311.
15. Marcus JN, Watson P, Page DL, Narod SA, Lenoir GM, Tonin P, Linder-Stephenson L, Salerno G, Conway TA, Lynch HT. Hereditary breast cancer; pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage. *Cancer* (1996) 77, 697-709.
16. Serova O, Narod SA, Tonin P, Feunteun J, Sylla B, Lynch HT, Lenoir GM. BRCA1 mutation analysis of 20 breast-ovarian cancer families. *American Journal of Human Genetics* (1996) 58, 42-51.
17. Lerman C, Narod S, Schulman K, Hughes C, et al. Predictors of utilization of BRCA1 testing in hereditary breast ovarian cancer families: implications for patient education and informed consent. *JAMA* (in press).
18. Durocher F, Tonin P, Shattuck-Eidens D, Skolnick M, Narod SA, Simard J. Mutation analysis of the BRCA1 gene in 24 families with cases of cancer of the breast ovary and multiple other sites *Mutation Res* (in press).
19. Tonin P and 26 others, incl. Narod SA. Frequency of recurrent BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer families. *Nature Med* (in press).
20. Serova O, Mazoyer S, Puget N, Dubois V, Tonin P, Shugart Y, Goldgar D, Narod SA, Lynch HT and Lenoir GM. Mutations in BRCA1 and BRCA2 in breast cancer families. Is there a third gene? *Am J Hum Genet* (submitted).